Exploring early interim analyses in basket designs in Oncology

Oliver Sailer, Anna Pöhlmann, Frank Fleischer

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Basket designs and Bayesian hierarchical model

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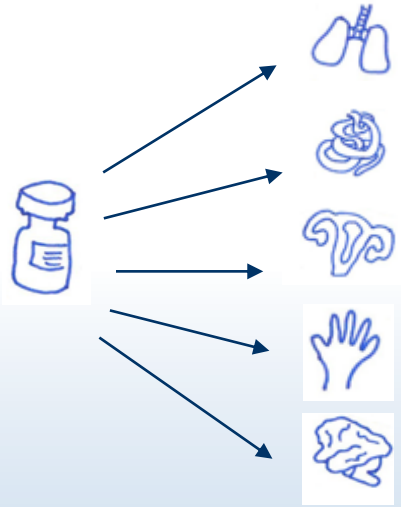
Basket designs

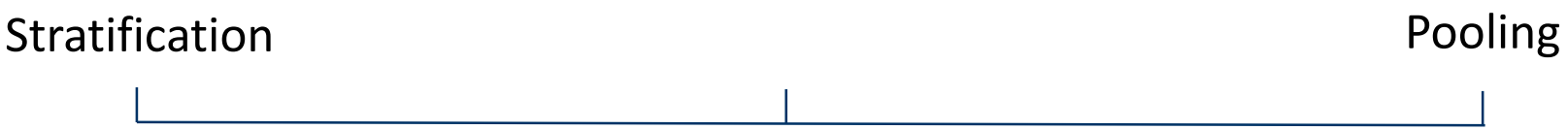
- Basket trial*
  - One experimental treatment
  - (Patients with similar genomic features)
  - Different disease types (Renfro and Sargent, 2016)

- Questions
  - Does the treatment work sufficiently?
  - Can we identify cohorts with a promising effect?



* Renfro and Sargent (2016)

Basket designs - analysis approaches



- Assumes independent cohorts
- Low precision

- Assumes the same underlying response rate in all cohorts
- Potentially large bias

Bayesian hierarchical model (BHM)

- Assumes exchangeability between cohorts
- Parameter of between-cohort variation determines the extent of borrowing

BHM adjusting for target rate (Berry et al., 2013)

- Random cohort effect in terms of log-odds of response rate
- Likelihood

$$r_i | p_j \sim Bin(p_j, n_j)$$

$$\theta_j = log\left(\frac{p_j}{1-p_j}\right) - log\left(\frac{\tilde{p}_j}{1-\tilde{p}_j}\right)$$

Exchangeability of log-odds after adjusting for target rates

- Prior

$$\theta_j | \mu, \tau \sim N(\mu, \tau^2)$$
$$\mu \sim N(m_\mu, v_\mu)$$
$$\tau \sim HN(s_\tau)$$

Informative prior on between-cohort variability; scale parameter choice see Neuenschwander et al. 2015

- Implementation: R interface to JAGS, R2JAGS package

Recruitment and analysis strategies

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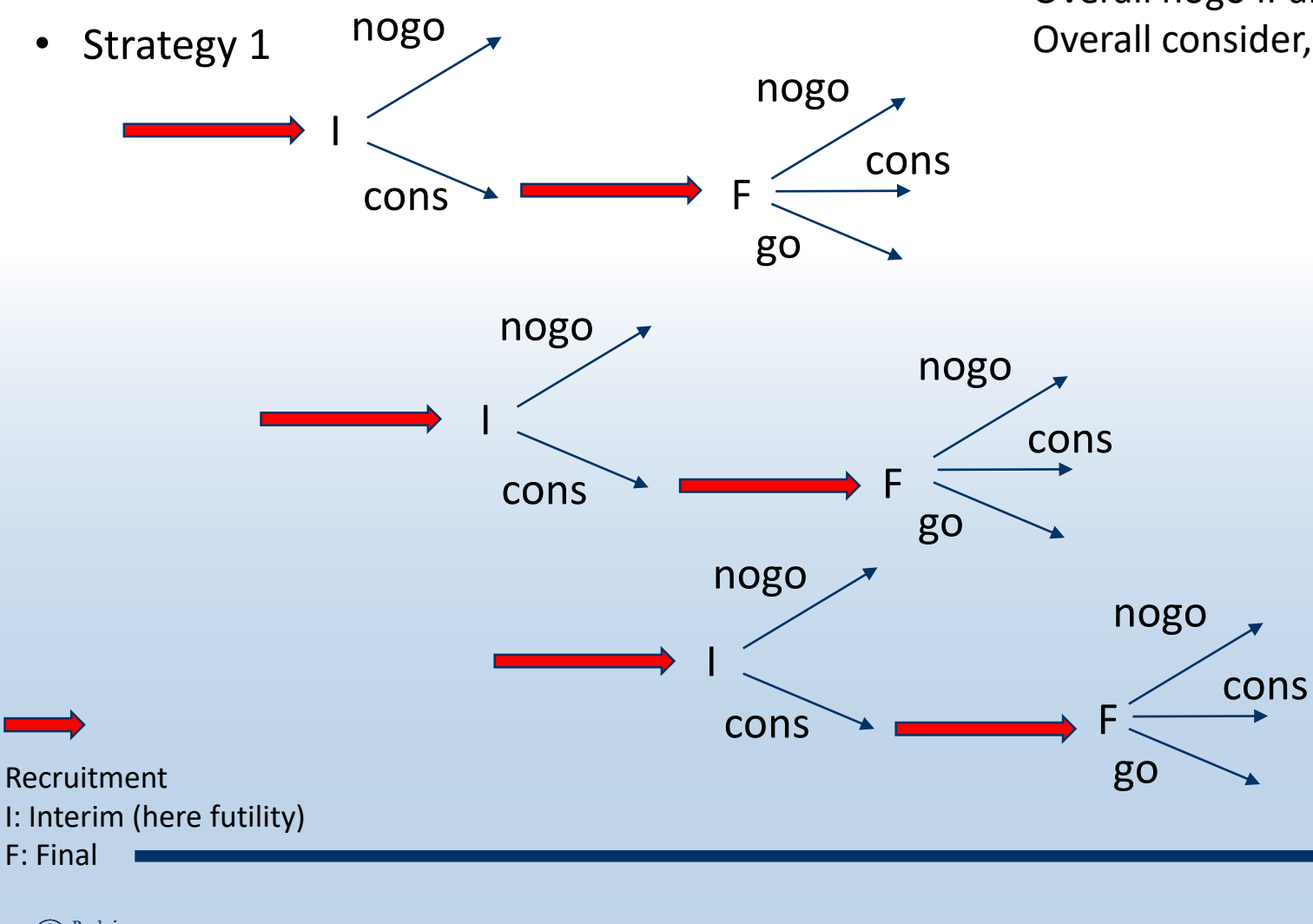
Recruitment and analysis strategies

- Interim analyses performed to limit exposure of additional patients to an ineffective drug
- Futility could be based on within-cohort analysis only or borrow information across cohorts
- Possible consequences of futility
  - Stop recruitment into cohort
  - Do not develop drug further for cohort (no-go)
  - Exclude cohort from later analyses (“test-then-pool”, Viele et al. 2013)

Recruitment and analysis strategies

Overall go at first cohort go
Overall nogo if all cohorts nogo
Overall consider, else

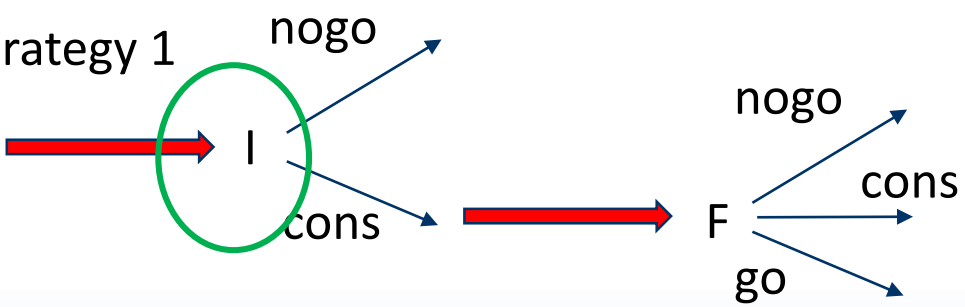
- Strategy 1

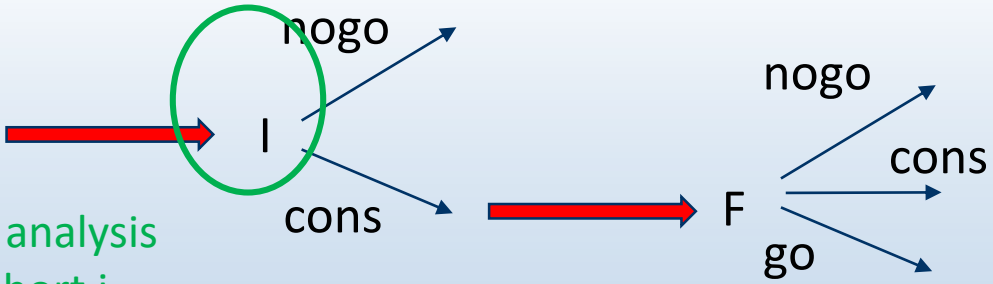


Recruitment and analysis strategies

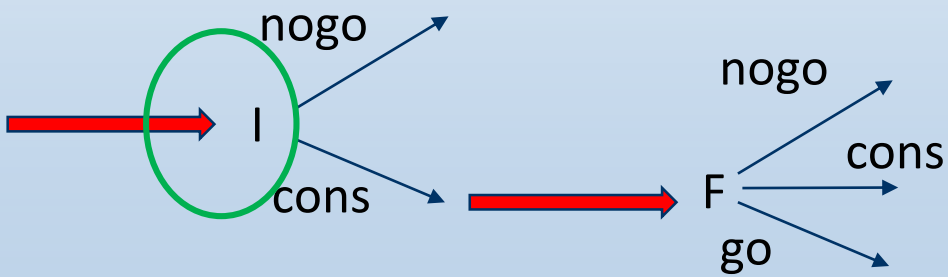
Overall go at first cohort go
Overall nogo if all cohorts nogo
Overall consider, else

- Strategy 1





Interim futility analysis
Decision for cohort i
use only data of cohort i
nogo if <r responders



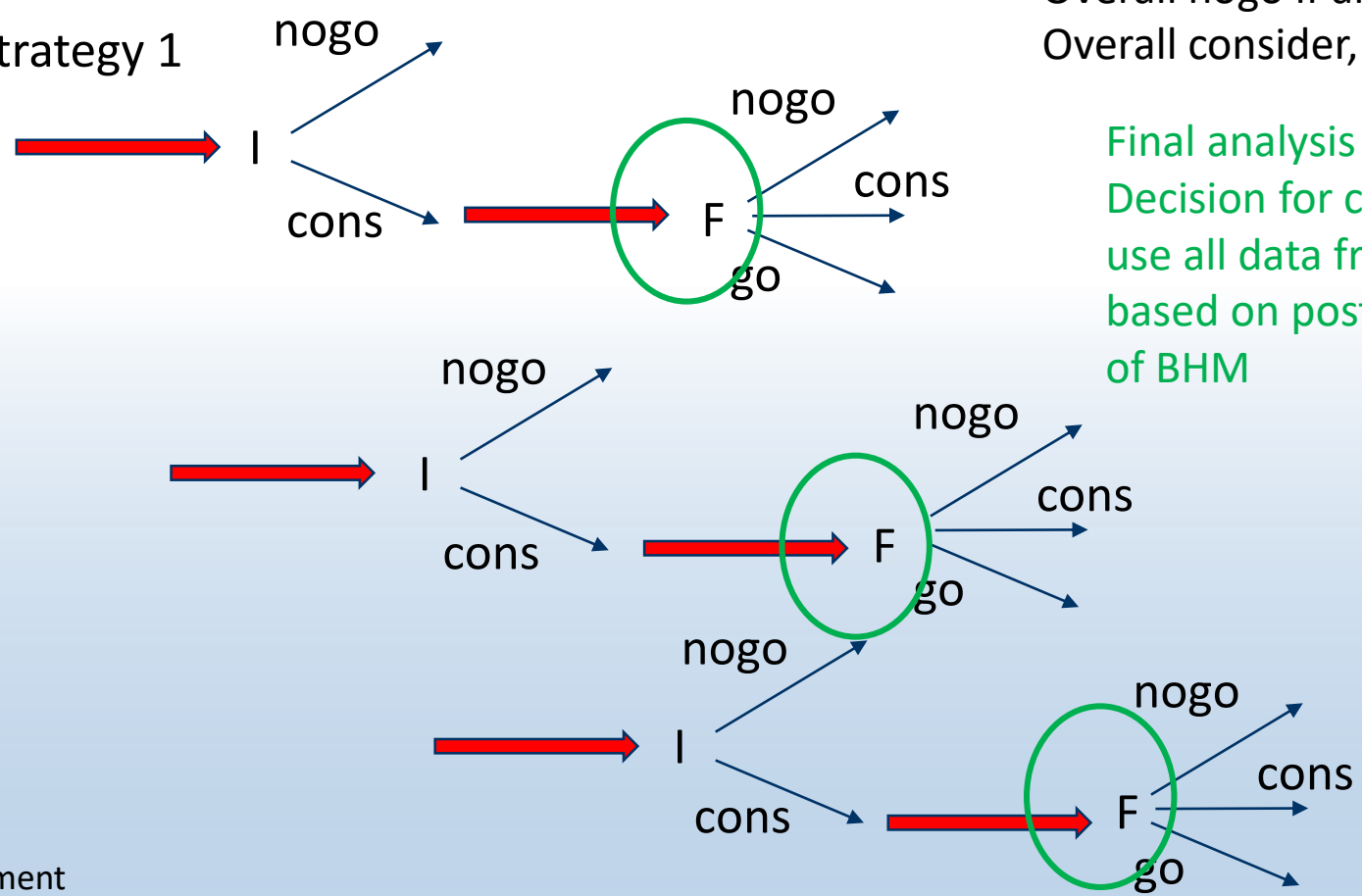
Recruitment
I: Interim (here futility)
F: Final

Time

Recruitment and analysis strategies

Overall go at first cohort go
Overall nogo if all cohorts nogo
Overall consider, else

- Strategy 1

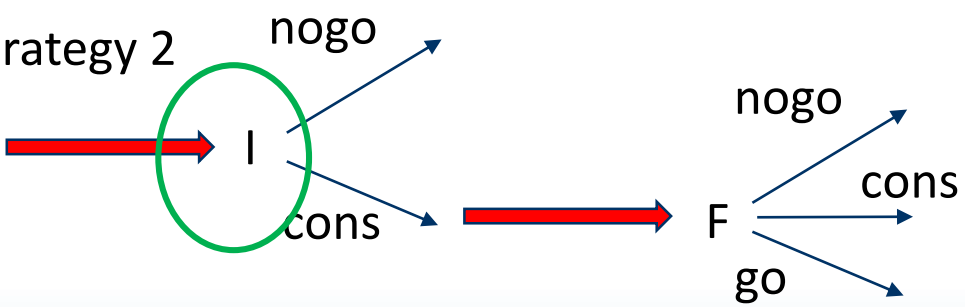


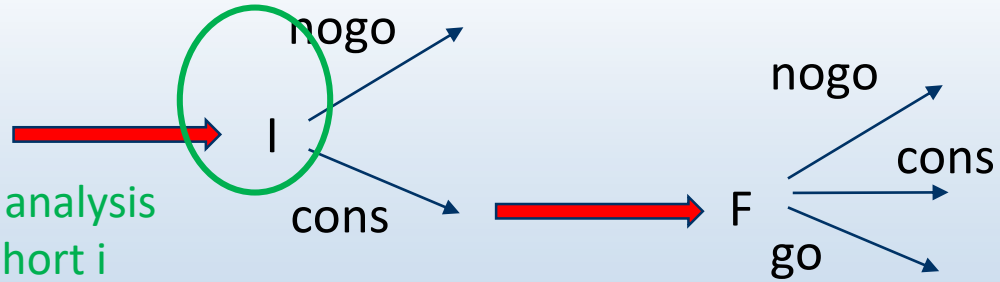
Final analysis
Decision for cohort i
use all data from all cohorts
based on posterior
of BHM

Recruitment and analysis strategies

Overall go at first cohort go
Overall nogo if all cohorts nogo
Overall consider, else

- Strategy 2





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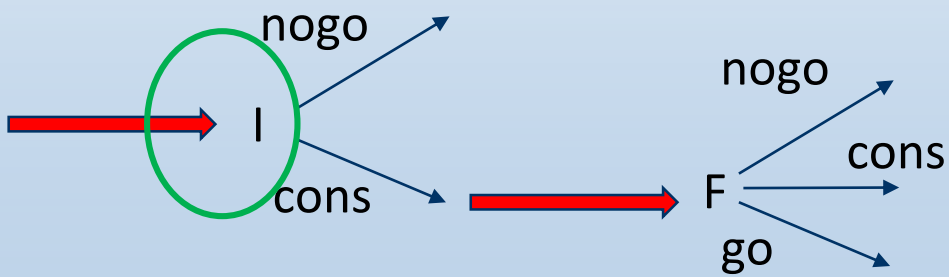


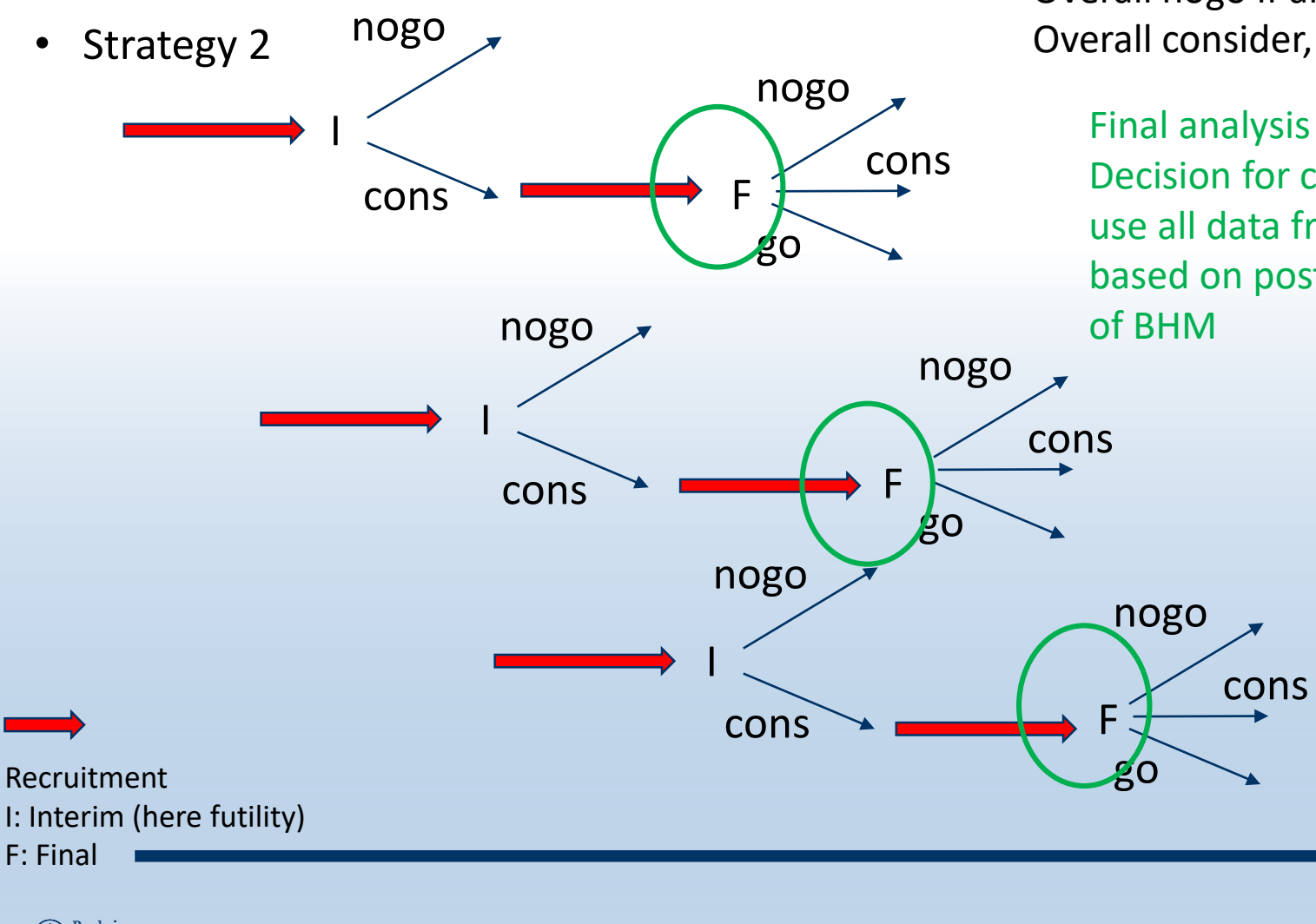
Recruitment
I: Interim (here futility)
F: Final

Time

Recruitment and analysis strategies

Overall go at first cohort go
Overall nogo if all cohorts nogo
Overall consider, else

- Strategy 2

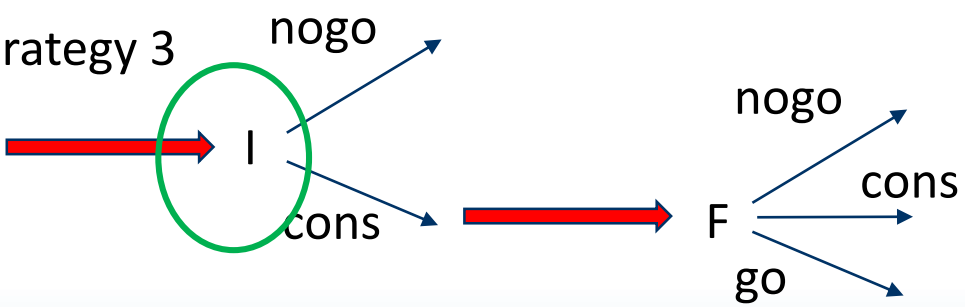


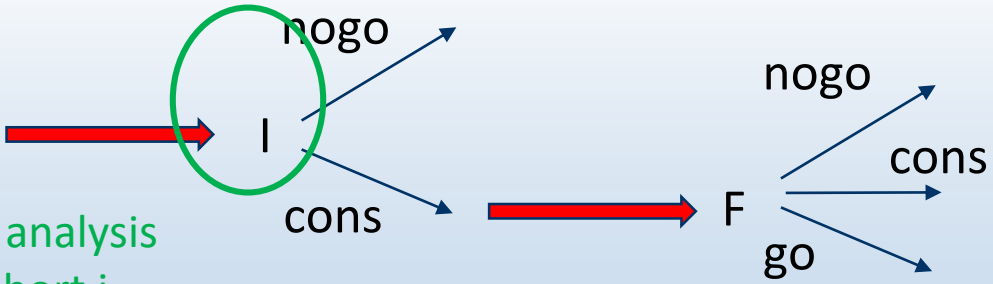
Final analysis
Decision for cohort i
use all data from all cohorts
based on posterior
of BHM

Recruitment and analysis strategies

Overall go at first cohort go
Overall nogo if all cohorts nogo
Overall consider, else

- Strategy 3





Interim futility analysis
Decision for cohort i
use only data of cohort i
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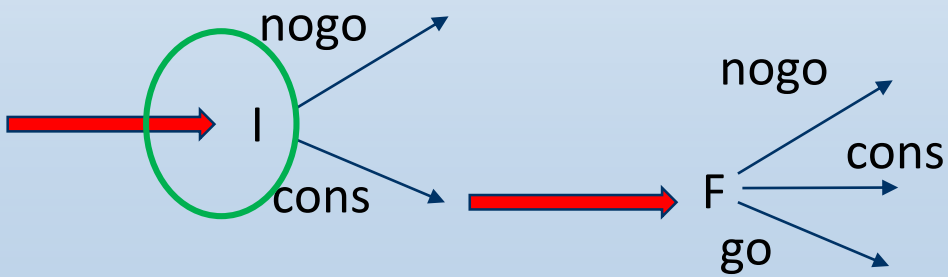


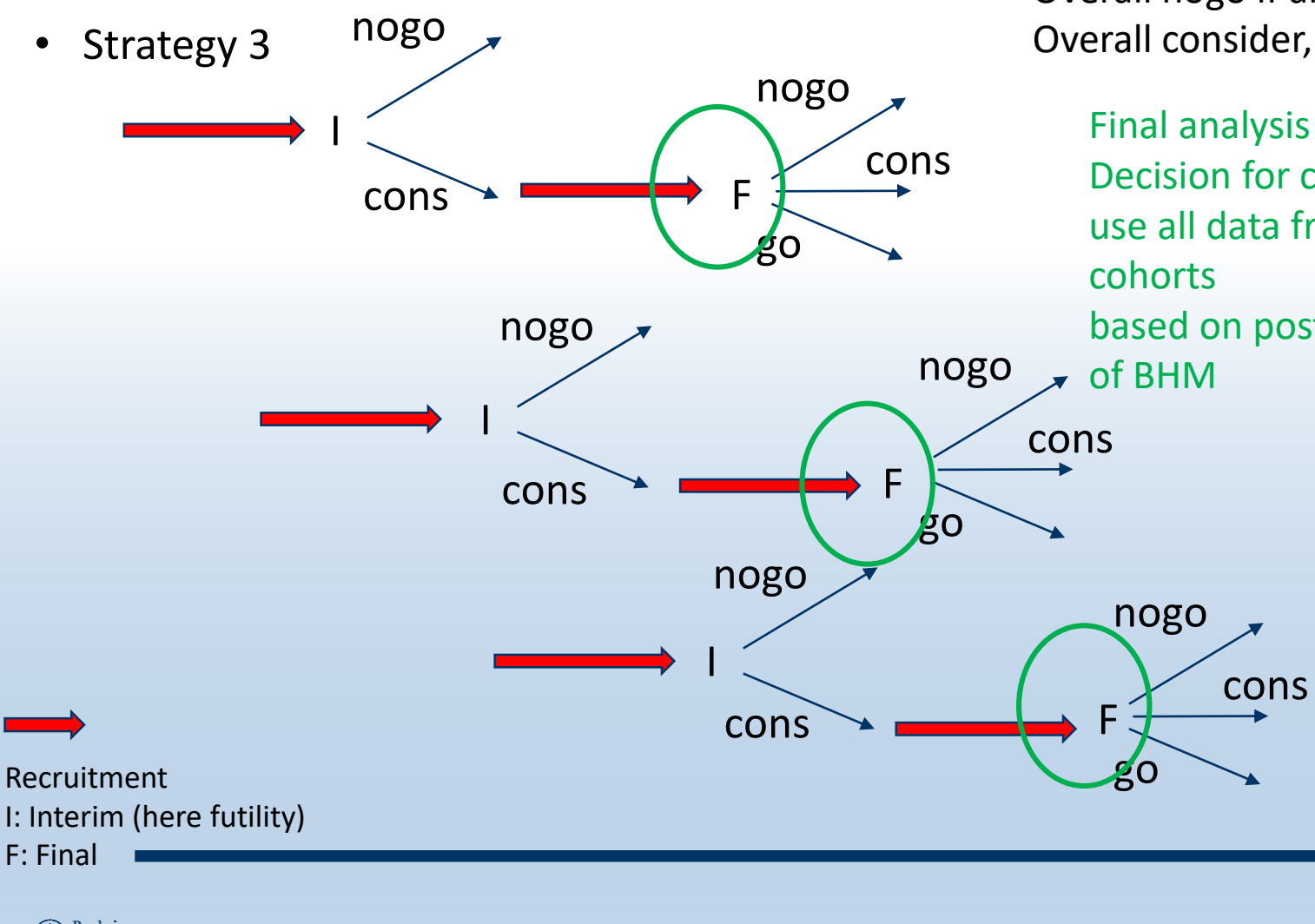
Recruitment
I: Interim (here futility)
F: Final

Time

Recruitment and analysis strategies

Overall go at first cohort go
Overall nogo if all cohorts nogo
Overall consider, else

- Strategy 3

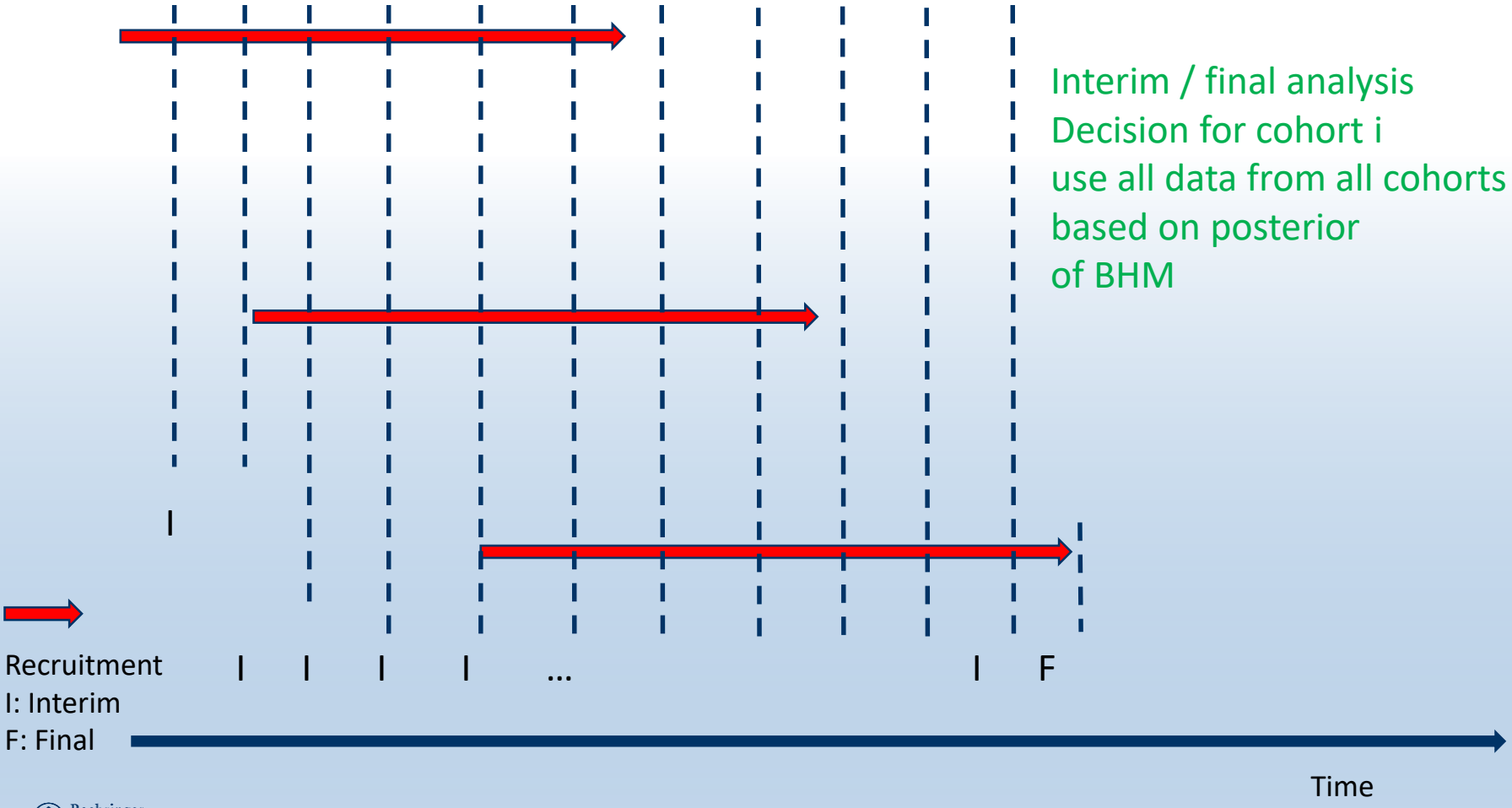


Final analysis
Decision for cohort i
use all data from non-futile cohorts
based on posterior of BHM

Recruitment and analysis strategies

- Strategy 4

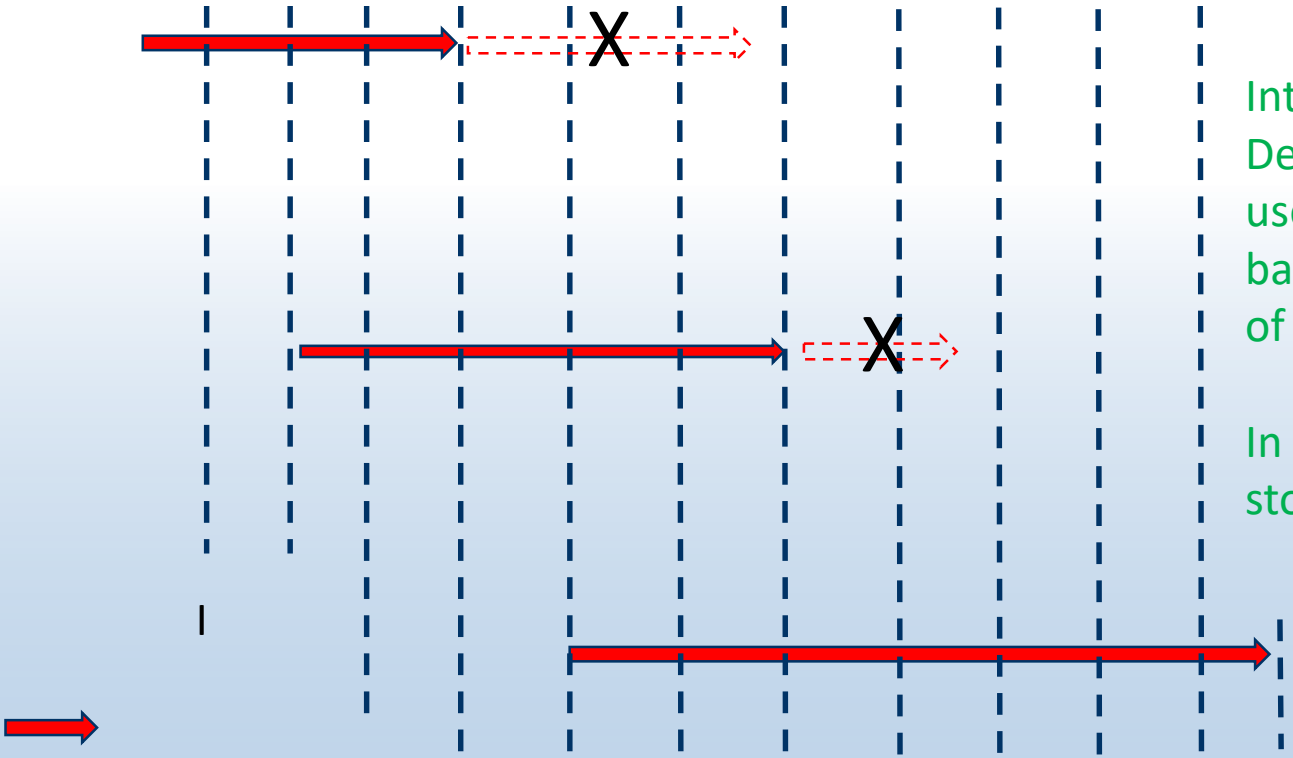
Overall go at first cohort go
Overall nogo if all cohorts nogo
Overall consider, else



Recruitment and analysis strategies

- Strategy 4

Overall go at first cohort go
Overall nogo if all cohorts nogo
Overall consider, else

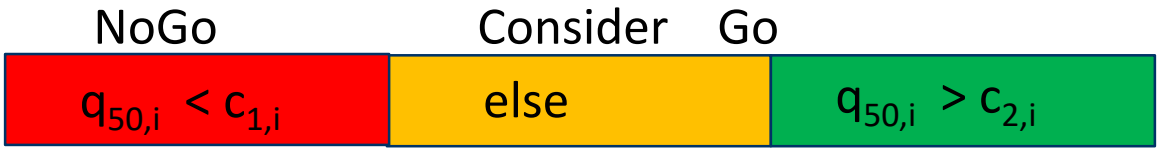


Interim / final analysis
Decision for cohort i
use all data from all cohorts
based on posterior
of BHM

In case of interim futility,
stop recruitment for cohort

Model-based decision rule

Cohort i



$q_{50,i}$ median posterior response rate cohort i

$c_{1,i}, c_{2,i}$ cohort specific decision boundary

Variation

$q_{\gamma,i}$ γ-quantile of posterior distribution

Recruitment and analysis strategies

- Strategy 1-3: Futility after 10 patients, final after 20 (per cohort)
- Strategy 4: Interim analysis every 5 patients, Final at 4*20 max.

Response scenarios

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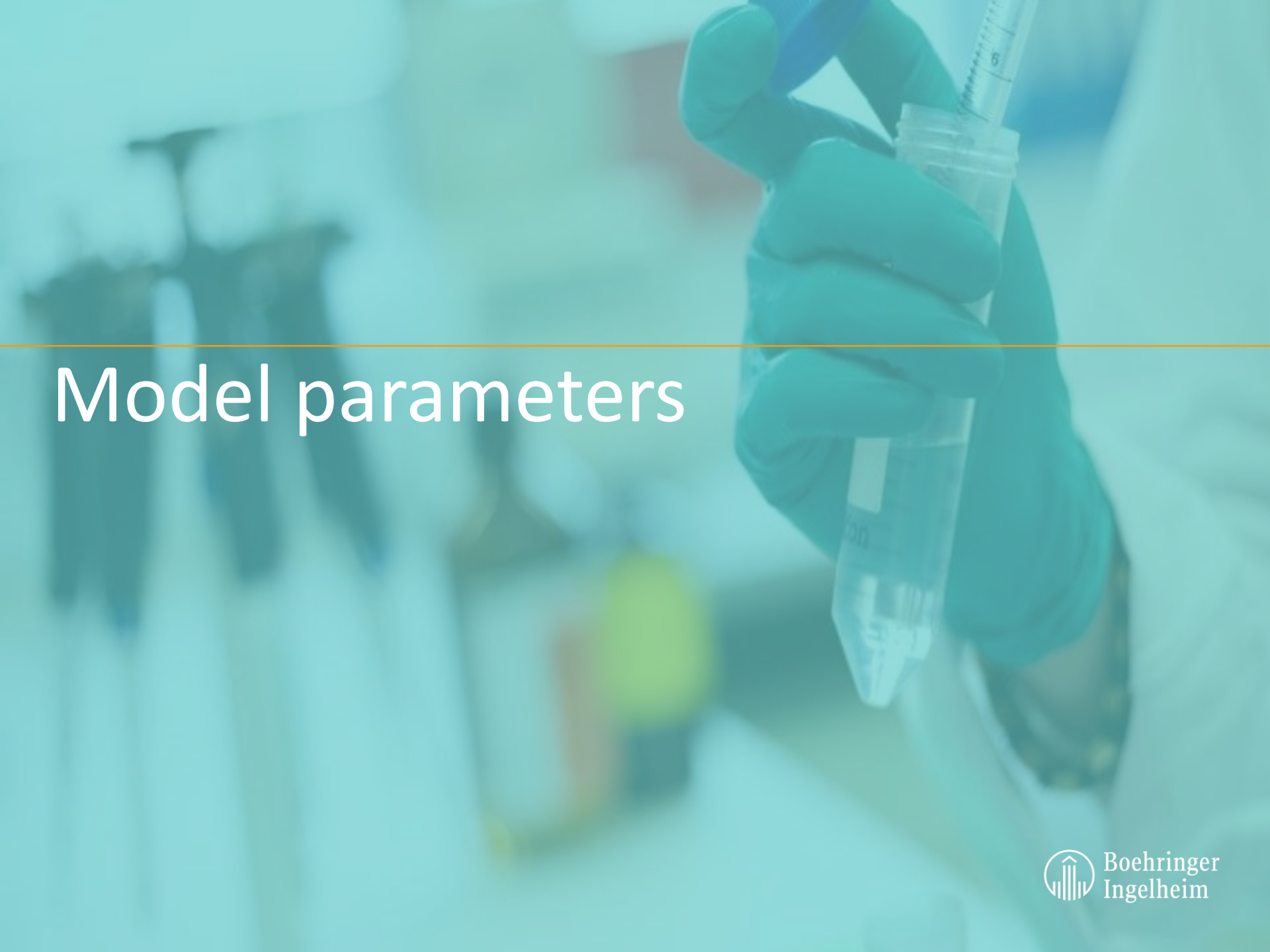
Response scenarios

- Positive and negative scenarios
- Positive nugget scenario
- Mixed response scenario

	Sc. 1	Sc. 2	Sc. 3	Sc. 4
Cohort 1	40%	15%	40%	40%
Cohort 2	40%	15%	15%	40%
Cohort 3	25%	10%	10%	10%
Cohort 4	25%	10%	10%	10%

Model parameters



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Model parameters

- Model adjustment parameter $\tilde{p}_j$
- Controls borrowing
- Target rate by cohort set to assumed response rate if drug works (as in Berry et al 2013)

- Inter-cohort variability prior $\tau \sim HN\ (s_\tau)$
  - $scale$ = 0.5 allows for range of τ up to substantial heterogeneity

Operating characteristics

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Operating characteristics

- Decision probabilities in scenarios
- Average sample size and duration

Simulation results

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Scenario 1

Strategy	NoGo	Consider	Go	N	t
1	0 1/2/9/5	15 24/25/23/22	85 75/73/68/73	66	9.1
2	0 1/5/5/5	15 24/22/26/22	85 75/73/69/73	66	9.1
3	0 1/2/9/5	14 23/24/23/21	86 76/74/68/74	66	9.1
4	0 1/5/5/5	15 24/22/26/22	85 75/73/69/73		3.4
4V	0 1/2/9/5	14 23/24/23/21	86 76/74/68/74		4.7

NoGo, Consider, Go: Probability in %, N average number evaluable, t average duration (months)

Scenario 2

Strategy	NoGo	Consider	Go	N	t
1	60 72/76/86/84	39 28/24/14/15	1 0/0/0/1	68	11.5
2	74 81/84/90/88	25 19/16/10/11	1 0/0/0/1	64	9.0
3	48 65/69/80/77	50 35/31/20/21	2 0/0/0/2	68	11.5
4	74 81/84/90/88	25 19/16/10/11	1 0/0/0/1		4.3
4V	48 65/69/80/77	50 35/31/20/21	2 0/0/0/2		6.0

NoGo, Consider, Go: Probability in %, N average number evaluable, t average duration (months)

Scenario 3

Strategy	NoGo	Consider	Go	N	t
1	4 6/53/60/64	71 70/46/36/32	25 24/1/4/4	68	11.2
2	16 18/57/67/65	60 59/42/29/31	24 23/1/4/4	73	10.4
3	1 2/44/48/55	60 62/55/47/40	39 36/1/5/5	67	11.0
4	16 18/57/67/65	60 59/42/29/31	24 23/1/4/4		4.1
4V	1 2/44/48/55	60 62/55/47/40	39 36/1/5/5		6.4

NoGo, Consider, Go: Probability in %, N average number evaluable, t average duration (months)

Scenario 4

Strategy	NoGo	Consider	Go	N	t
1	2 3/5/43/48	36 51/46/50/41	62 46/49/7/11	66	10.2
2	4 9/1/42/45	35 47/42/51/44	61 44/48/7/11	72	10.1
3	0 1/5/38/45	31 46/37/52/41	69 53/58/10/14	66	10.0
4	4 9/1/42/45	35 47/42/51/44	61 44/48/7/11		3.7
4V	0 1/5/38/45	31 46/37/52/41	69 53/58/10/14		5.9

NoGo, Consider, Go: Probability in %, N average number evaluable, t average duration (months)

References

- Berry SM, Broglio KR, Groshen S, and Berry DA (2013): Bayesian hierarchical modeling of patient subpopulations: efficient designs of phase II oncology clinical trials. Clinical Trials, 10(5), 720-734.
- Neuenschwander B, Wandel S, Roychoudhury S, Bailey, S (2015): Robust exchangeability designs for early phase clinical trials with multiple strata. Pharmaceut. Statist. 15, 123–134.
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- Viele K, Berry S, Neuenschwander B et al. (2014): Use of historical control data for assessing treatment effects in clinical trials. Pharmaceutical Statistics 13, 41-54.

Questions?

Optional subtitle

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